REMARKS

In the Office Action dated September 15, 2008, Claims 1-47 are pending. Claims 28-29 are withdrawn from further consideration. Claims 1-27 and 30-47 are examined. Claims 17-19, 26 and 27 are objected to as improper multiple dependent claims. Claims 18 and 30 are also objected to for certain claim language. Claim 37 is rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-6, 8-27, and 30-47 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1, 2, 6, 8, 10, 11, 17, 19-25, 31, 35, 44, 45, and 47 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Chang et al. (*Nat. Immunol.* 2000, 1: 169-176). Claims 1-27 and 30-47 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimacher et al. (US 2002/0059652) in view of both Shaffer et al. (*Immunity*, 2002, 17: 51-62) and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307). The specification is objected to for certain informalities.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Specification

The specification has been amended to delete the extra term "functional" on page 66, lines 6-7, and to delete the symbols which appear on page 71, line 16.

The objection to the specification is therefore overcome and withdrawal thereof is respectfully requested.

Claim Amendments

Independent claim 1 has been amended to more clearly define the genetic modification as comprising "the insertion of a reporter molecule-encoding sequence into an allele of the endogenous *Blimp (PRDM-1)* gene", which results in a modified *Blimp* allele. Support for this amendment is found throughout the specification, e.g., on page 6, lines 21 to 25, page 20, line 20, and page 44, lines 12 to 29. Independent claims 20, 30 and 44 have been amended in a similar manner.

Claims 1, 2, 20, 30, 31, 44 and 45 have also been amended to delete the references to or non-functional part, form, homologue, and variant of Blimp-1. Claims 6-7 and 35-36 have been canceled without prejudice.

Other amendments have been made to change claim dependencies and/or clarify claim language.

No new matter is introduced by the foregoing amendments.

Claim Objections

Claims 17-19, 26 and 27 are objected to as improper multiple dependent claims. Claims 18 and 30 are also objected to for certain unclear claim language.

It is respectfully submitted that these objections have been fully addressed by the foregoing amendments. Withdrawal of the objections is therefore respectfully requested.

35 U.S.C. §112, Second Paragraph

Claim 37 is rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The recitation of "genetic materials" in claim 37 allegedly lacks antecedent basis.

It is respectfully submitted that the rejection is obviated in view of the amendment to claim 37. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. §112, First Paragraph

Claims 1-6, 8-27, and 30-47 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner's rejection is directed to the aspect of the claims relating to functional part, form, homologue, and variant of Blimp-1.

Applicants respectfully submit that the claims have been amended to delete references to functional or non-functional part, form, homologue, and variant of Blimp-1. Accordingly, it is believed that the written description rejection is overcome, and withdrawal thereof is respectfully requested.

35 U.S.C. §102(b)

Claims 1, 2, 6, 8, 10, 11, 17, 19-25, 31, 35, 44, 45, and 47 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Chang et al. (*Nat. Immunol.* 2000, 1: 169-176).

Chang allegedly teaches modified U937 cells (i.e., human macrophage precursors) comprising a modified *blimp-1* gene which encodes a fusion protein between the wild type Blimp-1 polypeptide and GFP. The presence of Blimp-1 within the cells was monitored via GFP expression, and wherein the expression of Blimp resulted in terminal differentiation of U937 cells to macrophages.

Applicants observe that the modified U937 cells taught by Chang over-expressed an exogenous modified Blimp, T-Blimp. Chang further teaches the over-expression of exogenous Blimp as part of a retroviral bicistronic vector which also allows concurrent expression of GFP.

The objective of the study by Chang was to determine whether expression of Blimp-1 was sufficient to drive macrophage differentiation. Chang found that overexpression of Blimp-1 was sufficient to *induce* macrophage differentiation. However, Applicants respectfully submit that neither the expression of exogenous Blimp nor the expression of GFP in Chang is under the control of endogenous *Blimp* regulatory sequences.

In contrast, the present invention is based on the determination of the expression level of *Blimp-1*as indicative of the stage of terminal differentiation of a cell. A principal feature of the invention is to determine the expression level of *endogenous Blimp-1*, and the reporter gene is placed under control of *Blimp-1* regulatory elements in order to recapitulate *endogenous Blimp-1* expression. See the paragraph bridging pages 64-65. This feature of the present invention is quite distinct from Chang, where *exogenous Blimp-1* was introduced to achieve overexpression and to *cause* terminal differentiation. Chang does not teach how to detect endogenous Blimp protein expression through insertion of a reporter gene into an endogenous *Blimp* allele, as presently claimed.

Accordingly, Applicants respectfully submit that Chang does not teach the claimed invention. The rejection under 35 U.S.C. §102(b) based on Chang is overcome. Withdrawal thereof is respectfully requested.

35 U.S.C. §103(a)

Claims 1-27 and 30-47 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher et al. (US 2002/0059652) in view of both Shaffer et al. (*Immunity*, 2002, 17: 51-62) and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307).

Glimcher allegedly teaches transgenic mouse comprising a modified *xbp-1* gene encoding functional or non-functional XBP-1 polypeptide co-expressed with a selectable marker

or GFP. Glimcher also allegedly teaches using the transgenic mouse or B- or T-cells obtained from the mouse to screen for agonists or antagonists of terminal differentiation of B- or T-cells. Glimcher does not teach genetically altering the *Blimp-1* gene. However, the Examiner notes that the reference teaches that XBP-1 transcription factor acts downstream of Blimp-1. Additionally, Shaffer allegedly teaches that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp-1 acts by allowing the expression of specific transcription factors such as XBP-1. Therefore, the Examiner concludes that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the cells and methods of Glimacher by substituting their *XBP-1* with *Blimp-1* to achieve the predictable result of obtaining genetically modified cells comprising modified *Blimp-1* as presently claimed.

Applicants respectfully disagree.

The problem to be solved by the present invention is how to detect terminal differentiation of haematopoietic cells. The solution is provided by the targeted insertion of a reporter sequence into the endogenous *Blimp* gene sequence. In contrast, the problem to be solved by Glimcher is how to regulate hepatocyte growth, plasma cell differentiation and T cell subset activity. The solution in Glimcher is provided by identifying agents which modulate XBP-1 by assessing a change in XBP-1 expression. There is no recognition by Glimcher that terminal differentiation of haematopoietic cells is linked to Blimp. Accordingly, those skilled in the art would not have even been motivated to look to Glimcher for a solution to the problem of detecting terminal differentiation of haematopoietic cells.

Further, Applicants observe that the genetically modified cells disclosed by Glimcher include animals/cells which lack XBP-1 (abstract and paragraphs [0004], [0011], [0083], [0091], [0178] and [0214]), have over-expressed XBP-1 in conjunction with a reporter gene responsive

to the XBP-1 protein (paragraphs [0006] and [0214]), have over-expressed XBP-1 (paragraphs [0031], [0053], [0068] and [0073]), have an XBP-1 transgene driven by a liver-specific promoter (paragraph [0011]), or have an altered XBP-1 (paragraph [0082]). There is no disclosure or suggestion in Glimcher of a modified *Blimp* gene being endogenous *Blimp* inserted with a reporter driven by endogenous *Blimp* regulatory elements, as presently claimed. Again, because there is no recognition by Glimcher that terminal differentiation of cells is linked to Blimp, those skilled in the art would not have even been motivated to place a reported gene under control of endogenous *Blimp* regulatory elements, as presently claimed, in order to detect endogenous *Blimp* expression as indication of terminal differentiation.

Furthermore, the Examiner has combined Glimcher with Schaffer and indicated that by using the cells and methods of Glimcher and substituting the XBP-1 gene with Blimp-1, those skilled in the art would have achieved the invention. Applicants respectfully submit that modifying the cells and methods of Glimcher, as suggested by the Examiner, would result in the generation of a knockout Blimp mouse or cells lacking Blimp-1. See the abstract and paragraphs [0004], [0011], [0083], [0091], [0178] & [0214] of Glimcher). Alternatively, one would obtain (1) cells which over-express Blimp-1 in conjunction with a reporter gene responsive to the Blimp-1 protein (paragraphs [0006] and [0214]); (2) cells which over-express Blimp-1 (paragraphs [0031], [0053], [0068] and [0073]); (3) cells which have a *Blimp-1* transgene driven by a liver-specific promoter (paragraph [0011]), or (4) cells which have an altered Blimp-1 (paragraph [0082]) in contrast to wild type Blimp-1. However, none of these alternatives would provide a cell or non-human organism comprising such a cell containing a genetic modification characterized by the insertion of a reported gene in an endogenous *Blimp-1* allele, as presently claimed.

Therefore, Applicants respectfully submit that Glimcher does not provide a motivation for those skilled in the art to achieve the claimed invention; and even if, *pro arguendo,* the skilled person did use those cells and methods of Glimcher and substituted XBP-1 with Blimp-1, the skilled person would still not obtain the cell with the genetic modification as presently claimed.

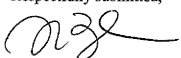
The secondary references to Schaffer and Mountford do not cure these fundamental deficiencies of Glimcher. Applicants respectfully submit that the cited references taken in combination do not teach or suggest the feature of the genetically modified cell as presently claimed, i.e., an *endogenous* Blimp-1 allele is modified with the insertion of a reporter sequence wherein expression of the polypeptide comprising the reporting molecule that is expressed from the modified allele is under the control of *endogenous Blimp* regulatory elements.

Therefore, it is respectfully submitted that the claimed invention is not obvious in view of the combination of Glimacher, Shaffer and Mountford. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser, P. C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
Telephone: 516-742-4343
XZ:ab